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State of the Art Review

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Recent Advances in Chronic Thromboembolic Pulmonary Hypertension: Expanding the Disease Concept and Treatment Options

Sung-A Chang, MD, PhD[1], Jeong Hoon Yang, MD, PhD[1], Dong Seop Jung, MD, PhD[2], and Nick H. Kim, MD[3]

[1]Division of Cardiology, Department of Internal Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[2]Division of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[3]Division of Pulmonary, Critical Care, and Sleep Medicine, University of California San Diego, La Jolla, CA, USA

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Correspondence to
Sung-A Chang, MD, PhD
Division of Cardiology, Department of Medicine, Pulmonary Hypertension Center, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81, Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
Email: elisabet.chang@gmail.com

Nick H. Kim, MD
Division of Pulmonary, Critical Care, and Sleep Medicine, University of California San Diego, 9300 Campus Point Drive, MC7381, La Jolla, CA 92037, USA.
Email: h33kim@health.ucsd.edu

ORCID iDs
Sung-A Chang
https://orcid.org/0000-0001-5124-605X
Jeong Hoon Yang
https://orcid.org/0000-0001-8138-1367
Dong Seop Jung
https://orcid.org/0000-0002-6947-8403

AUTHOR'S SUMMARY

Chronic thromboembolic pulmonary hypertension (CTEPH) is a severe form of pulmonary hypertension characterized by obstructive clots in pulmonary arteries, leading to elevated pressure and heart failure. This review discusses the progression in understanding and treating CTEPH, highlighting the importance of improved diagnostic methods and advanced therapeutic options such as pulmonary endarterectomy and balloon pulmonary angioplasty. It emphasizes the significance of a multidisciplinary approach in managing the disease, which has significantly enhanced patient outcomes by integrating surgical, interventional, and medical therapy.

ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive form of pulmonary hypertension characterized by unresolved thromboembolic occlusion of pulmonary arteries, leading to increased pulmonary arterial pressure and right heart failure. This review examines recent advances in the pathophysiology, diagnosis, and management of CTEPH, focusing on expanding disease concepts and evolving therapeutic approaches. The incidence of CTEPH has been revised upward with improved diagnostic techniques revealing a higher prevalence than previously recognized. Advances in surgical and interventional therapies, particularly pulmonary endarterectomy and balloon pulmonary angioplasty, have significantly improved outcomes. Emerging medical therapies, including pulmonary vasodilators like riociguat, have offered new hope for inoperable cases.
The understanding of CTEPH has broadened, leading to better diagnostic strategies and more comprehensive treatment options that significantly enhance patient outcomes. Multidisciplinary team approaches are crucial in managing the disease effectively.

Keywords: Chronic thromboembolic pulmonary hypertension; Chronic thromboembolic pulmonary disease; Balloon pulmonary angioplasty; Pulmonary endarterectomy

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Nick H. Kim
https://orcid.org/0000-0003-4702-650X

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INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a treatable form of pulmonary hypertension (PH) associated with chronic obstruction of the pulmonary arteries following pulmonary embolism (PE). CTEPH incidence has been estimated around 5–6 cases per million per year, however when systemic follow-up was instituted for acute PE patients, incidence was increased to 13 cases per million habitants in registry data from Europe.[1)]

Following the early phase of acute pulmonary thromboembolism (PTE), unresolved blood clots gradually transform into fibrotic tissue, creating new layers within the pulmonary vessels and forming obstructive lesions. The thromboembolism may disrupt the endothelial cells, which become intermingled with the thrombus, leading to the development of endothelial dysfunction. For this reason, organized mural thrombus (chronic fibrotic clots) cannot be resolved by anticoagulation. These chronic obstructive changes reduce blood flow in the pulmonary arteries, which in turn promotes the progression of local thrombus formation. Obstructive pulmonary vessels also develop secondary vasculopathy with features similar to that observed in pulmonary arterial hypertension (PAH).[2)] Therefore, residual PH from vasculopathy can remain even after removal of chronic thromboembolism. The combination of the mechanical obstruction and the small vessel disease contribute to the worsening of PH and right ventricular (RV) failure, which ultimately can lead to death.

Treatment of CTEPH has been traditionally limited to complex surgery which removes the chronic thrombus and the mechanical component of disease within the pulmonary arteries. However, with the development of medical and interventional therapy, there has been dramatic revolution in the management of CTEPH especially within the past decade. Here, we review these recent developments in CTEPH including diagnosis, evolving treatment, and recommendations from recent guidelines and expert international consensus.

CONCEPT OF DISEASE FROM CTEPH TO EXTENDED DISEASE GROUP

CTEPH is defined as a condition in which symptoms are due to obstruction of pulmonary arteries by chronic, organized fibrotic clots, leading to PH. According to the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines, CTEPH is diagnosed by cardiac catheterization with hemodynamic criteria of a mean pulmonary arterial pressure (mPAP) ≥25 mmHg, a mean pulmonary arterial wedge pressure <15 mmHg, and a pulmonary vascular resistance (PVR) ≥3 Wood units (WU).[3)] There is also a subset of patients who present with similar chronic fibrotic clots in the pulmonary arteries and experience symptoms, but who do not meet the hemodynamic thresholds for CTEPH. These patients often have limited exercise capacity due to a combination of exercise-induced PH and increased dead space ventilation, impacting their quality of life.[4)]

Those patients have been identified as having “chronic thromboembolic disease” (CTED) by researchers.[5)] However, this term does not specify the affected lesion as being in the pulmonary arteries, and there was a need for a broader term that encompasses the spectrum of diseases originating from chronic PTE. To address this, “chronic thromboembolic pulmonary disease” (CTEPD) was proposed by Task Force members of the 2021 ERS statement on CTEPH.[6)]

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CTEPD is defined as symptomatic patients who exhibit mismatched perfusion defects on ventilation/perfusion (V/Q) lung scans and evidence of chronic clots on computed tomography pulmonary angiography (CTPA) or conventional pulmonary angiography, and regardless of the presence of PH at rest. This expanded concept was also adopted by the 2022 ESC/ERS guidelines. Thus, CTEPD serves as a broader disease category, with CTEPH remaining as a specific designation for patients within the CTEPD group who have confirmed PH.[7][8] Additionally, the definition of PH was revised following the 2018 World Symposium on Pulmonary Hypertension (WSPH), which lowered the normal mPAP threshold from <25 mmHg to ≤20 mmHg, and subsequently the PVR threshold from 3 WU to 2 WU. These updates have also been incorporated into the recent ESC/ERS guidelines.

DIAGNOSTIC CONSIDERATION FOR CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

The diagnosis of CTEPH typically begins with the detection of PH through echocardiography in patients presenting with dyspnea, with dyspnea on exertion being the most common symptom. In advanced cases, symptoms of RV failure may also develop. Echocardiography is a practical tool for assessing PH, and further differential diagnosis of PH is essential for confirming CTEPH.

A V/Q lung scan is the recommended and valuable first step for the diagnosis of CTEPD (**Figure 1**).[9] A perfusion scan alone can still provide useful information if a ventilation scan is unavailable. Additionally, combined imaging with single-photon emission computed tomography (CT) is advantageous for localizing affected areas, as it offers 3-dimensional visualization of lung parenchyma (**Figure 2**). However, a high-probability V/Q scan alone cannot confirm a diagnosis of CTEPH, as other pulmonary vascular diseases may present similarly. These include pulmonary arterial tumors, vasculitis, peripheral pulmonary arterial stenosis,[10] pulmonary vein stenosis, pulmonary veno-occlusive disease, acute PE, and extrinsic compression of pulmonary arteries, such as from anthracofibrosis (**Figure 3**).[11]

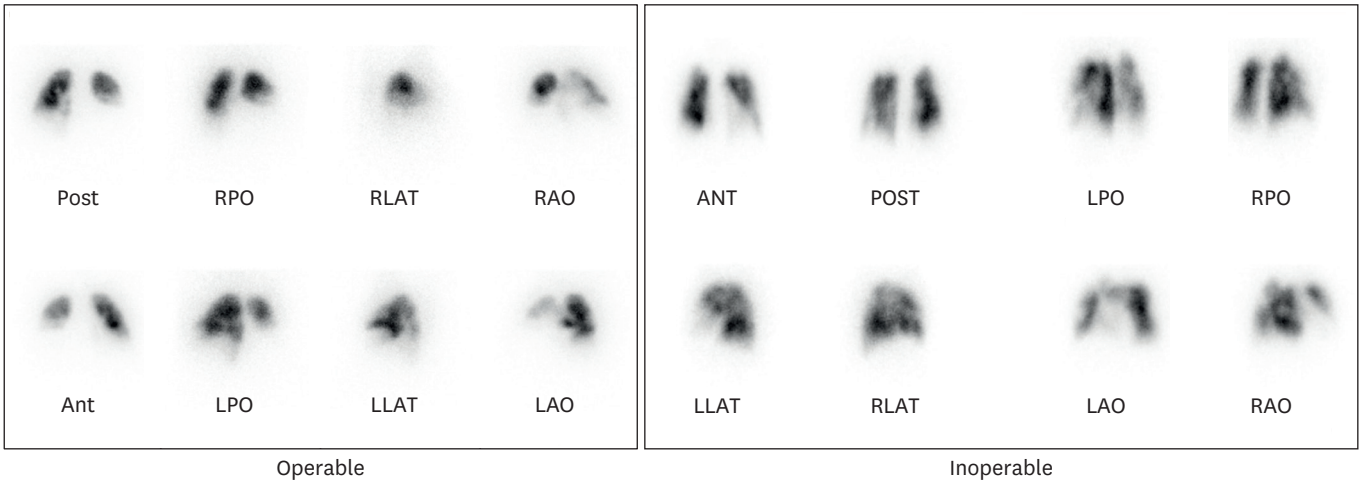

Figure 1. Lung perfusion scan comparison of operable vs. inoperable CTEPH. The right panel initially identified as idiopathic pulmonary arterial hypertension, was ultimately diagnosed as inoperable CTEPH with primarily distal subsegmental lesions.
ANT = anterior; CTEPH = chronic thromboembolic pulmonary hypertension; LAO = left anterior oblique; LLAT = left lateral; LPO = left posterior oblique; POST = posterior; RAO = right anterior oblique; RLAT = right lateral; RPO = right posterior oblique.

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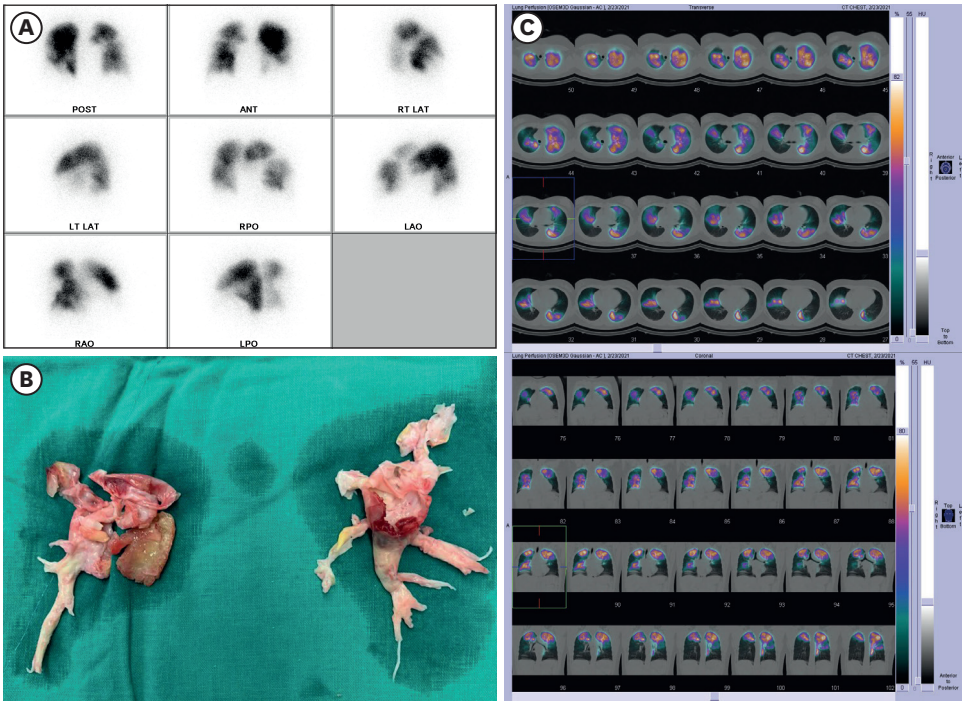

Figure 2. Lung perfusion SPECT provides enhanced anatomical information, demonstrating its utility in detailed vascular imaging. (A) Lung perfusion scan; (B) Surgical specimen; (C) Lung SPECT.
ANT = anterior; LAO = left anterior oblique; LPO = left posterior oblique; LTLAT = left lateral; POST = posterior; RAO = right anterior oblique; RPO = right posterior oblique; RTLAT = right lateral; SPECT = single-photon emission computed tomography.

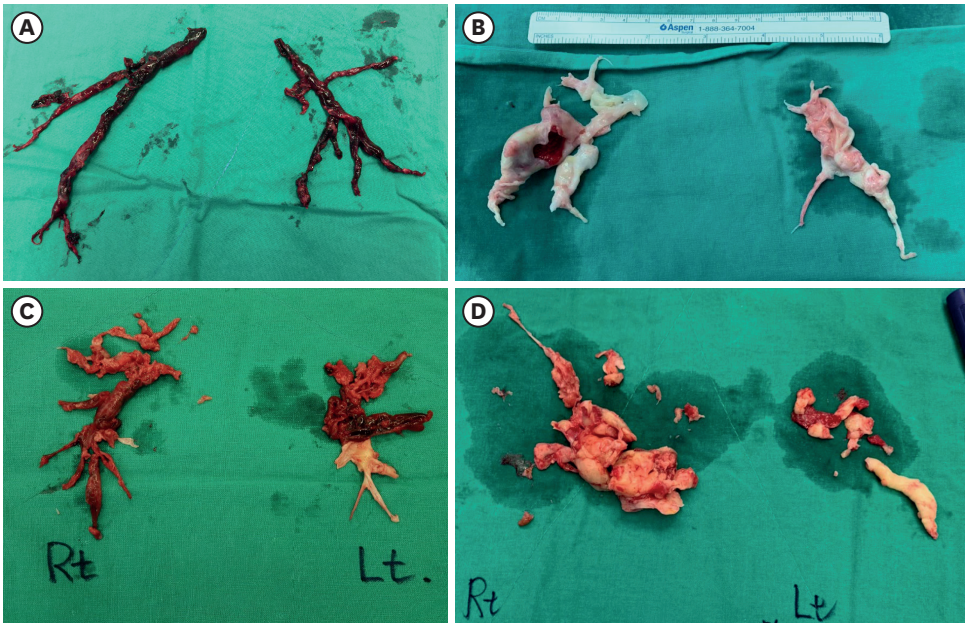

Figure 3. Not all obstructive lesions in pulmonary arteries are due to chronic thromboembolic pulmonary hypertension. Differentiation from acute pulmonary thromboembolism or tumors is essential before surgery.
(A) Acute pulmonary embolism; (B) Chronic thromboembolic disease; (C) Acute on chronic thromboembolism; (D) Pulmonary artery sarcoma.

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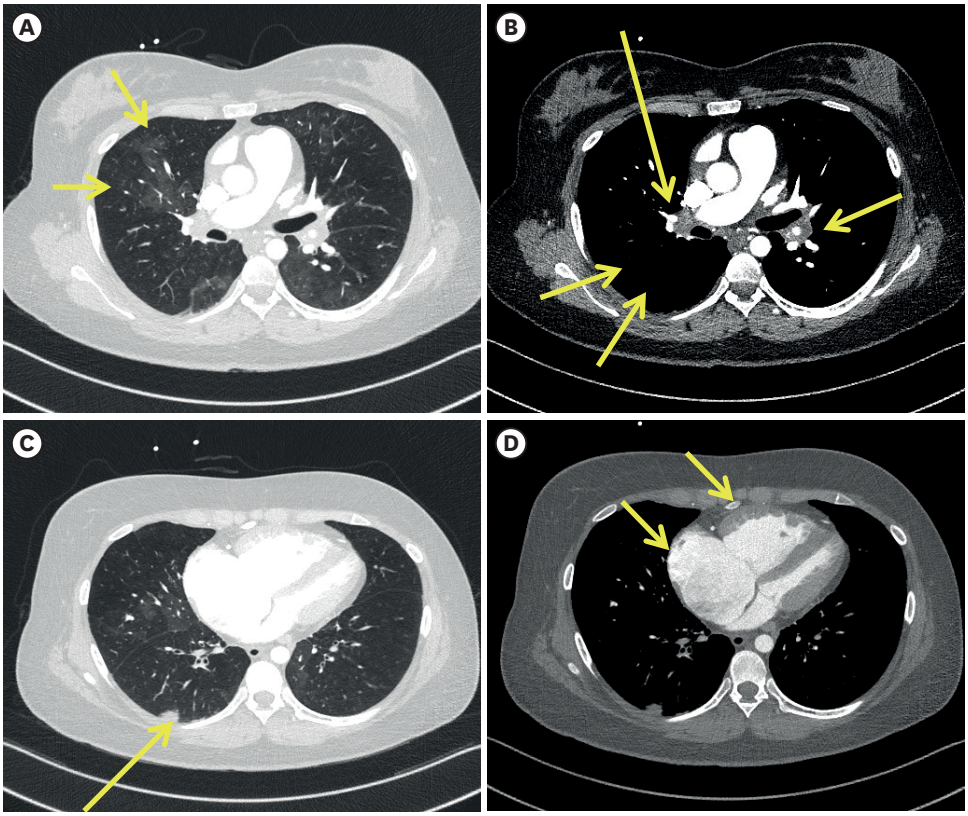

Figure 4. Typical computed tomography angiography features in chronic thromboembolic pulmonary hypertension patients. (A) Mosaic pattern of lung parenchyma; (B) Reduced visibility of distal vessels, calcified thrombi, and chronic thrombi; (C) Lung infarction; (D) Enlargement of the right atrium and ventricle, deviation of left ventricular septum.

CTPA is an essential test for evaluating CTEPH, although its diagnostic sensitivity is generally slightly lower than that of the V/Q scan, which is why it is not recommended as a primary screening tool in ESC/ERS guidelines. However, CTPA is more accessible in many centers and offers high accuracy for detecting proximal CTEPH lesions (**Figure 4**). It is also useful for differentiating CTEPH from other pulmonary obstructive diseases, as it provides information on lung parenchymal changes and other specific features of CTEPH.

CTPA can reveal characteristic signs of CTEPH, such as mural thrombus, intravascular webs, arterial narrowing or retraction, and complete arterial occlusion. Other indicators, such as bronchial artery hypertrophy, a mosaic lung pattern, and lung infarction, are also commonly observed in CTEPH. However, peripheral CTEPH can be challenging to detect on CTPA, and subtle changes in distal vessels and lung parenchyma may require interpretation by an experienced radiologist. Advanced imaging techniques like dual-energy CT can enhance visualization of the pulmonary arteries by using iodine perfusion maps, and studies have reported dual-energy CT to have 97% sensitivity and 86% specificity for diagnosing CTEPH.[12] Additionally, cone-beam and area-detector CT have been shown to improve visualization of the pulmonary vasculature and can assist in guiding balloon pulmonary angioplasty (BPA) procedures.[7] Despite these advancements, clinical practice often varies from research settings, and it is not uncommon for initial referral diagnoses to change following further evaluation, such as with a lung perfusion scan, repeated CT scan, or invasive pulmonary angiography at an expert center, shifting from idiopathic PAH to a diagnosis of CTEPH.

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Magnetic resonance imaging (MRI) can visualize pulmonary vessels without radiation exposure, making it an attractive option. However, its use in diagnosing CTEPH in clinical practice is limited due to longer scan times, limited access to specialized expertise, and constraints in post-scan reconstruction. MRI is particularly valuable for assessing RV function, making it a useful tool for evaluating RV performance in patients with CTEPH.

Pulmonary angiography is time-tested and accurate diagnostic method for assessing the morphology of the pulmonary arteries, and in many expert centers, deemed essential for determining treatment options and planning surgical or interventional procedures. Image acquisition should be performed using biplane cine fluoroscopy at specialized centers to ensure precise visualization. However, because it is an invasive procedure, pulmonary angiography is recommended selectively, typically for cases where treatment planning requires detailed anatomical assessment after non-invasive evaluations.

RECENT ADVANCES IN CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION TREATMENT

New paradigm of chronic thromboembolic pulmonary hypertension treatment and multidisciplinary team approach

Pulmonary endarterectomy (PEA) is the treatment of choice and remains the most effective option for operable CTEPH cases. However, some cases are considered inoperable due to the risk of surgical inaccessibility of distal lesions. Furthermore, residual PH after PEA continues to pose a challenge, even in expert centers, and may affect long-term survival of patients.

Over the past decade, CTEPH management has evolved into new treatment paradigms that extend beyond surgery, incorporating medical therapy (newer anticoagulation and pulmonary vasodilators) and interventional therapy, namely BPA. The first pulmonary vasodilator specifically for CTEPH was approved in 2013,[13] and the importance of a multidisciplinary team (MDT) approach was emphasized at the 5th WSPH in 2013, held in Nice.[14]

In 2012, a Japanese group reported single-center clinical data on the safety and efficacy of BPA,[15-17] which was later recognized as "an important component of the CTEPH treatment algorithm" at the 6th WSPH.[18] Given the complexity of CTEPH and the diversity of available treatments, a MDT approach has become essential for optimal management. The CTEPH Task Force Report from the 7th WSPH outlined a structured approach to recovery in CTEPH, summarized in **Table 1** and **Figure 5**.

Although robust scientific evidence from well-designed studies on the MDT approach in CTEPH is limited, this approach is widely accepted and increasingly recognized as essential at experienced CTEPH centers worldwide. The growing number of personalized treatment options for CTEPH underscores the importance of a collaborative team. Both the expert statements from the past WSPH and the 2022 ESC/ERS PH Guidelines reinforced

Table 1. Steps to recovery in chronic thromboembolic pulmonary hypertension: AMEND[19]

A	**A**nticoagulation
M	**M**ultidisciplinary team review
E	**P**ulmonary endarterectomy
N	**N**onsurgical treatments: medical therapy, balloon pulmonary angioplasty
D	**D**on't forget follow-up assessment after any intervention

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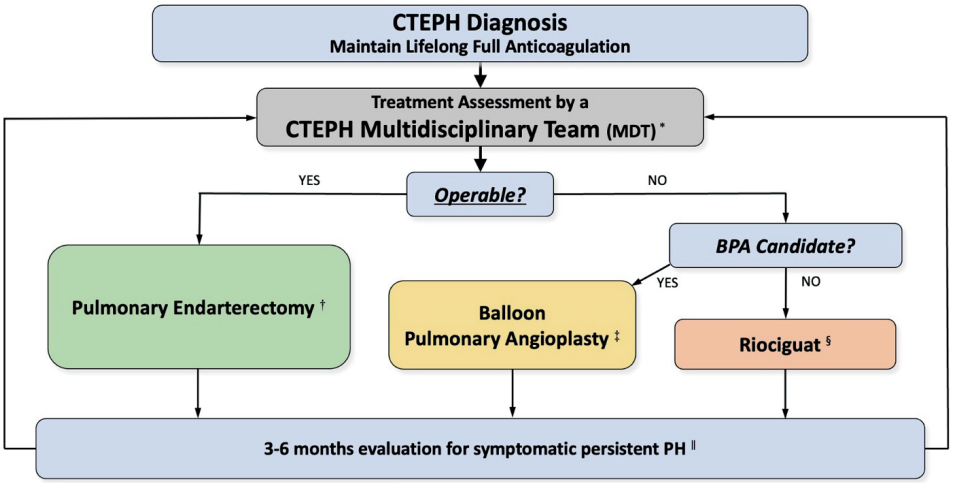

Figure 5. CTEPH treatment algorithm as suggested by the 7th World Symposium on Pulmonary Hypertension CTEPH working group.[19]
BPA = balloon pulmonary angioplasty; CTEPH = chronic thromboembolic pulmonary hypertension; MDT = multidisciplinary team; mPAP = mean pulmonary arterial pressure; PEA = pulmonary endarterectomy; PH = pulmonary hypertension; PVR = pulmonary vascular resistance.
*CTEPH MDT requires pulmonary endarterectomy surgeon, PH expert, BPA specialist and chest radiologist.
†Treatment of choice for technically operable disease.
‡Riociguat therapy prior to BPA: mean pulmonary arterial pressure ≥40 mmHg or pulmonary vascular resistance >4 Wood units.
§Other PH medications approved in select regions.
‖Structured follow-up; may include imaging and hemodynamic assessment.

this concept, recommending that MDTs include PEA surgeons, BPA interventionalists, PH specialists, and thoracic radiologists, all trained in high-volume centers to optimize patient outcomes.[8] While all guidelines and recommendations emphasize the absence of randomized or well-designed studies on this topic,[3)6-8)19)] they acknowledge that a MDT approach is increasingly seen as a requirement for expert centers. This collaborative model is deemed essential for achieving optimal results for CTEPH patients.

At the 7th WSPH, the role of CTEPH MDT was outlined as follows; (1) confirmation of CTEPH diagnosis; (2) determination of operability; (3) determination of BPA potential; (4) determination of appropriateness of medical therapy and/or multimodal approach; and (5) follow-up/review of previously treated patients to assess the need for additional therapy and to provide feedback for the MDT.[19] It is also recommended that the ideal MDT should include 2 clinicians from each interventional subspecialty to facilitate a range of perspectives and ensure comprehensive decision-making.

Pulmonary endarterectomy

Surgical resection of chronic thrombotic material in pulmonary vessels is a critical component of PEA. In experienced centers, the surgery is safe and effective with a mortality rate of less than 2% and with rapid, often dramatic improvement in PH. In the previous era, before the advent of riociguat and BPA, PEA was the sole treatment option for CTEPH and significantly enhanced patient survival. In cases where patients were deemed inoperable or did not undergo surgery, the 3-year survival rate for CTEPH was only about 70%.[20]

Currently, the survival rates for patients undergoing PEA are impressive, with over 90% surviving at 3 years, 87% at 5 years, and 78% at 10 years. According to the CTEPH registry from international global registry, patients treated with PEA and BPA had significantly lower mortality

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rates (7% and 11%, respectively) compared to those without either mechanical intervention (27%). The observed 3-year survival rates for PEA, BPA and only medically treated groups were 94%, 92%, and 71% ($p<0.001$), respectively.[19)21)] These improvements for the inoperable group can largely be attributed to the introduction of therapies like BPA and riociguat, which have expanded treatment options and enhanced patient outcomes in recent years.

Reperfusion lung injury and airway hemorrhage are potential but serious complications associated with PEA. Severe diseases characterized by high PVR is a recognized risk factor. However, recent outcomes from expert centers indicate that postoperative mortality rates are now below 5%, suggesting that high PVR alone should not be considered a contraindication for surgery.

Advancements in extracorporeal membrane oxygenation (ECMO) technology have enhanced postoperative management for high-risk patients, allowing for optimized hemodynamic support during the perioperative period. Reperfusion lung injury and mild transient airway hemorrhage can be managed with supportive care, and if needed longer time on mechanical ventilation support. However, more severe airway bleeding can occur in 2–3% of cases, necessitating additional ECMO support.[22)]

RV failure with residual PH is less common and is usually associated with incomplete surgical resection or cases with severe concomitant small vessel disease distal to limits of endarterectomy. In such instances, management may involve waiting for recovery from reperfusion injury while providing support with ECMO.[23)] If incomplete surgical outcomes or recurrent thromboembolism persist, rescue BPA has been anecdotally described (**Figure 6**).[24)] Residual PH associated with persistent RV failure, often combined with severe lung injury, remain leading causes of in-hospital mortality following PEA. Earlier studies have shown that immediate postoperative pulmonary hemodynamics plays a critical role in outcomes; specifically, estimated PVR levels in the intensive care unit can significantly impact mortality rates. A PVR greater than 500 $dyn \cdot s \cdot cm^{-5}$ is associated with a mortality rate of 10.3%, while a PVR of less than 500 $dyn \cdot s \cdot cm^{-5}$ correlates with a much lower mortality rate of only 0.9%. This underscores the importance of careful postoperative management and monitoring of PVR in patients recovering from PEA.[25)]

The determination of operability for PEA largely hinges on the surgeon's skill and the experience of the treatment center. A learning curve is essential for improving expertise in PEA, which is directly related to the number of patients treated at a center. However, regional and national differences in healthcare systems can limit the patient volume at certain facilities, making it challenging to establish centers of excellence for CTEPH surgery.

The 7th WPHS suggested that a 3-step stratified for PEA center and Expert PEA center as mortality (<5% and <3%), surgical volume (≥20 per year and >50 per year), and availability of ECMO support if necessary.[19)] In addition, the capability of treating segmental and subsegmental disease was added to the expert PEA center. Moreover, expert centers also can provide other established treatments such as medical therapy and BPA according to the needs of individual cases.

Balloon pulmonary angioplasty

BPA was first reported in Europe in 1988,[26)] but early experiences, such as the Boston series, were associated with high complication rates.[27)] Since 2012, refinements led by centers in

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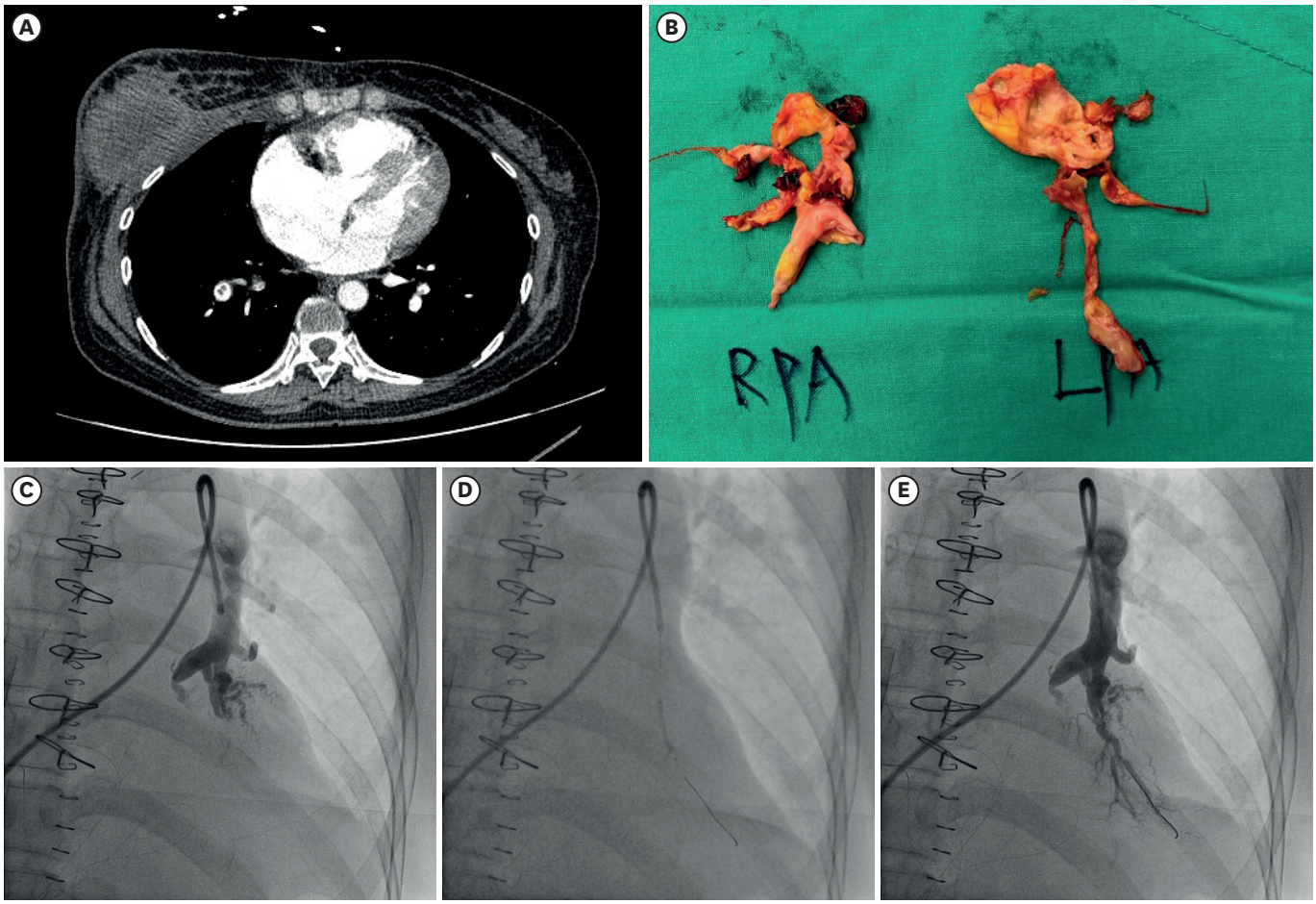

Figure 6. Case of rescue BPA following PEA. A 51-year-old woman with breast cancer and antithrombin III deficiency was admitted with acute pulmonary thromboembolism on a background of chronic thromboembolic pulmonary hypertension. Lack of response to anticoagulation and progressive disease necessitated emergency PEA. Post-PEA, high pulmonary arterial pressure persisted and cardiogenic shock progressed, requiring immediate ECMO support. After 2 sessions of BPA, she was successfully weaned from ECMO and discharged. (A) CT scan before surgery; (B) Surgical specimen from PEA; (C) Pulmonary angiography a week after PEA. Vascular obstruction is noted; (D) BPA was done for a targeted vessel; (E) Vascular beds are improved.
BPA = balloon pulmonary angioplasty; ECMO = extracorporeal membrane oxygenation; PEA = pulmonary endarterectomy.

Japan have significantly advanced the practice and medical evidence supporting BPA.[15-17] Initial reports from 2001 indicated a high incidence of complications associated with the procedure, which raised concerns about its safety. However, following modifications to BPA techniques by the Japanese center, subsequent experiences from other countries have demonstrated a lower complication rate along with clinical improvement in patients undergoing BPA.[28)29)]

At the 6th WSPH, BPA was recognized as "an important component of the CTEPH treatment algorithm"[18)] and is now considered a standard treatment for CTEPH or for patients experiencing residual PH after PEA, receiving a class IB recommendation.[8)] In certain cases where PEA is not feasible, BPA may be employed as an initial treatment method, further solidifying its role in the management of CTEPH.

In BPA, target lesions are visualized using pulmonary angiography, with careful lesion selection by the operator to maximize outcomes. Since BPA focuses primarily on segmental and subsegmental vessels, patients with a high disease burden may require multiple

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interventions to achieve optimal outcomes. The most common and important BPA complication is vascular injury associated with wire manipulation and ensuing hemoptysis and/or lung injury. In most cases, the injury is contained and manageable with supportive care. The rate of complication is both dependent on BPA experience of the operator and on severity of PH. Cases with high PAPs (>40 mmHg) and elevated PVR are at higher risk for vascular/lung injury.[30] Restenosis after BPA is rare, reported in only 0.6% of lesions over a median follow-up of 1.9 years.[31] Accordingly, stents are not used during BPA for CTEPH. Recent global studies (2018–2022) indicate an overall complication rate of about 7.7%, with a very low mortality rate of 0.8%.[32]

As with other complex procedures, safety and efficacy improve with operator experience, underscoring the importance of conducting BPA in expert centers. The 7th WSPH suggests that BPA centers should aim for at least 50 procedures annually with a procedure-related mortality rate under 3%. An "expert" BPA center is defined by a procedural volume of 100 cases per year, a mortality rate below 1%, and access to ECMO support to manage high-risk cases.[19]

BPA has also been utilized for patients who are technically operable but face challenges with PEA. While BPA can address surgically accessible lesions, its hemodynamic and functional benefits are generally less pronounced than those achieved with PEA alone. Nonetheless, BPA remains a valuable option in cases where patients cannot undergo PEA due to comorbidities, limited access to PEA centers, or a preference to avoid surgery.

In such cases, BPA serves as a viable alternative. Notably, survival rates following BPA at 1, 5, and 10 years post-procedure are comparable to those observed in PEA-treated patients.[33]

Given this, the 2022 ESC/ERS guidelines assign BPA a weaker recommendation (class IIbC) for technically operable patients, especially when they present predominantly distal disease or face an unfavorable risk-benefit ratio for surgery.[8] Ongoing trials are examining the long-term outcomes of both PEA and BPA. These studies are expected to provide valuable insights, which will help clarify BPA's role relative to PEA in the management of technically operable CTEPH patients who are unsuitable candidates for PEA. As these results emerge, they may lead to updated guidance on optimizing treatment for such patients, ensuring a more personalized approach to CTEPH management.[19]

BPA serves as a valuable adjunctive treatment for residual PH following PEA. BPA has shown a potential to improve hemodynamics and enhance exercise capacity in these patients. Evidence supporting a hybrid approach, combining BPA after PEA, is accumulating and appears promising for optimizing patient outcomes in challenging cases.[24][34][35] Moreover, preoperative BPA has been utilized in high-risk patients to reduce RV load, with reports indicating that this can lower perioperative risks and improve overall surgical outcomes.[36]

With the development of BPA, treatment options for CTEPH have expanded to include inoperable cases. Therefore, the decision-making process regarding surgery, intervention or a combination of both should be discussed within a MDT to determine the most appropriate treatment for each patients.

Medical therapy

Medical therapy plays a crucial role in preventing disease recurrence, improving hemodynamics, and enhancing physical activity in patients with CTEPH. This therapy

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typically involves life-long anticoagulation, management of RV failure, and the use of pulmonary vasodilators to improve vascular function and reduce PAP.

All patients with CTEPH are at high risk for recurrent thromboembolism and require continuous monitoring and lifelong anticoagulation therapy. Vitamin K antagonists (VKAs) have traditionally been the standard treatment for anticoagulation in CTEPH, and their use remains widely accepted in clinical practice.

In recent years, non-vitamin K oral anticoagulants (NOACs) have emerged as alternatives to VKAs for anticoagulation in many clinical scenarios. However, their use in CTEPH is still debated, and data regarding their efficacy and safety in this patient population are somewhat controversial. The choice of anticoagulant may differ depending on underlying conditions. For example, in patients with antiphospholipid syndrome (APLS), which accounts for approximately 10% of CTEPH cases, VKAs are recommended.[37][38] This highlights the importance of diagnosing APLS in patients with acute PE or CTEPH to guide the appropriate anticoagulant choice.

For most CTEPH patients, NOACs have been associated with an increased risk of recurrent PE, particularly in the postoperative period.[39] However, recent randomized trials have suggested that NOACs are not inferior to VKAs in terms of bleeding risk and recurrent PE incidence.[40] One explanation for the higher recurrence rates observed with NOACs could be persistent inflammatory conditions following surgery, which may increase the risk of thrombosis. Additionally, non-compliance with NOACs in real-world clinical settings could lead to rapid fluctuations in anticoagulant levels, increasing the risk of thrombogenicity. In contrast, VKAs tend to have a slower change in action and may offer more consistent protection against thrombosis in such cases.

Diuretics play a critical role in managing congestive symptoms of RV failure and cardiorenal syndrome in CTEPH patients. Particularly, they are essential for optimizing RV function, managing symptoms, and improving overall clinical status, especially before surgery or interventional procedures.

The use of diuretics such as loop diuretics (e.g., furosemide) and mineralocorticoid antagonists (e.g., spironolactone) is key to controlling symptoms and managing fluid balance. These medications help reduce RV workload by decreasing intravascular volume, which is crucial for improving cardiac output and alleviating symptoms like peripheral edema, ascites, and shortness of breath. Furosemide, especially when administered intravenously, is particularly useful in situations where there is gastrointestinal edema that may impair the absorption of oral diuretics. By providing rapid diuresis, intravenous furosemide helps to quickly reduce fluid overload and improve hemodynamics in acutely symptomatic patients, particularly in the perioperative setting. Proper management of diuretics ensures better volume control and supports recovery, facilitating smoother postoperative care and recovery following surgery or intervention.

Pulmonary vasodilators are studied because persistent PH after PEA is not fully explained by residual obstructive lesions. Long-standing hypoxia can induce vasoconstriction in pulmonary arteries and leads to the development of microangiopathy. Riociguat is the only medication approved by U.S. Food and Drug Administration (FDA) for CTEPH, backed by randomized controlled study that demonstrate improvements in functional capacity, PVR, and RV function.[13][41] Long-term outcomes also reveal the sustained effectiveness of riociguat

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in CTEPH.[42] Endothelin receptor antagonists have been explored to extend indications to CTEPH and have shown improvements in hemodynamics and exercise capacity, receiving approval in some countries, though they have yet to achieve FDA approval due to the limited scale of studies.[43][44] Subcutaneous treprostinil has yielded positive results in enhancing hemodynamics and exercise capacities, leading to its approval in select EU nations. However, a small randomized study of sildenafil did not show improvements in functional capacity.[45][46] Recently, the Phase III studies of selexipag and high-dose macitentan for inoperable CTEPH were discontinued due to futility.[19]

Currently, riociguat and BPA ought to be viewed as complementary rather than competing therapies for inoperable CTEPH.[47] RACE RCT has offered the strongest data in support of combining BPA and PH medical therapy, showing that introducing riociguat prior to BPA intervention can significantly reduce BPA complications. The new 7th WSPH CTEPD treatment algorithm recommends this combination treatment modality when treating more severe inoperable CTEPH cases.[48][49]

The use of PH medical therapy before PEA remains controversial and without supportive data. As such, the topic is not addressed in the recent guidelines. Expert consensus has been generally advising against surgery delays in operable cases.[50]

REGIONAL AND GLOBAL VARIATIONS IN CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION/ CHRONIC THROMBOEMBOLIC DISEASE TREATMENT

While PEA remains the most effective treatment for CTEPH when applicable, regional and global variations in the management of CTEPH and CTED are significant. The development of expert centers, crucial for delivering high-level care, depends on the long duration of a learning curve and the accumulation of experience. In many European countries, the CTEPH referral system is regulated by government policies, allowing for centralized practices. This centralization facilitates the development of expert centers, as it concentrates patient resources and medical professionals in a few locations, making it relatively easier to establish and maintain expert PEA centers—often only 1 or 2 per country. Conversely, in most Asian countries, the referral system for CTEPH is less controlled, and awareness and understanding of the disease have only recently begun to improve. This lack of centralized control and recent developments in disease recognition contribute to the absence of established expert centers in many parts of Asia, posing challenges to the standardization and enhancement of treatment protocols and outcomes.[51-54]

The underdiagnosis of CTEPH appears to be more common in Asian countries compared to Western nations, especially considering the rising total number of venous thromboembolism and PTE cases.[55] The development of BPA initially stemmed from a need for alternative interventions in Japan, due to limited resources for PEA. Presently, BPA is preferred in Japan for a broader range of CTEPH patients, despite the availability of PEA surgeons than European countries.

In the context of deciding between PEA and BPA, often referred to as the “grey zone,” Japanese clinicians typically classify distal segmental PA involvement as falling within this zone. However, this definition is subjective as leading Western centers refer to subsegmental PA involvement as the grey area.[56]

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The annual number of PEA procedures reported from Asian countries generally remains well below those from Western nations,[51-54] highlighting significant regional variations in the operability assessment for PEA. Additionally, access to treatments such as riociguat is constrained in some regions due to a lack of regulatory approval or inadequate insurance coverage. When formulating guidelines for CTEPH, it is crucial to evaluate the existing medical infrastructure and capabilities of each center and country.

Referring patients to more experienced centers is crucial when local facilities do not qualify as definitive "expert centers." This practice not only improves patient outcomes but also helps in fostering expertise by centralizing patient care. The development of several expert centers in the U.S., where there are no government-initiated dedicated CTEPH centers, illustrates the effectiveness of this approach. Centralizing care in this manner facilitates the accumulation of specialized knowledge and skills, which can significantly enhance the treatment and management of CTEPH.[57] This strategy emphasizes the importance of directing patients to specialized CTEPH centers as a crucial step towards cultivating expertise and establishing expert centers within their own countries.

CHALLENGES AND UNMET NEEDS IN MANAGING CHRONIC THROMBOEMBOLIC DISEASE AND CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

The diagnosis of CTED has broadened to include cases without PH, presenting a challenge in determining appropriate treatment protocols for these patients. Exercise-induced PH is frequently observed in CTED,[58] and RV dysfunction during exercise is noted in this demographic.[59] The mild degree and heterogeneity of symptoms in this population necessitate further investigation to develop specific treatment guidelines.

Currently, it is unclear how many patients with CTED will progress to CTEPH and whether early intervention could prevent this progression. However, a recent study by Reddy et al.[60] examined the natural history of CTEPD in 113 patients categorized by mean pulmonary artery pressure (mPAP ≤20 mmHg vs. 21–24 mmHg), finding no significant disease progression over a median follow-up of 37 months, suggesting that rapid progression may not be a typical feature in this population.

Moreover, there are potentially other candidate medications and combination strategies for targeting the pulmonary microcirculation that have not yet been studied. Despite advances with currently available CTEPH therapies, there remain CTEPH patients for various reasons not able to receive an established treatment such as PEA or BPA (Delcroix 24 Circulation). Accordingly, additional studies including novel treatment options are necessary to further expand our treatment landscape.

For now, the decision-making process between PEA and BPA often encounters a "grey zone" where it is not clear which approach is optimal for an individual CTEPH patient. The continued development and refinement of both interventional and surgical techniques are essential for providing more precise and personalized treatment solutions.

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CONCLUSION

Recent advancements in the diagnosis and treatment of CTEPH have led to better patient outcomes. The expansion of the disease concept to include CTEPD has improved the management of both CTEPH and milder cases. New diagnostic tools and treatments, such as pulmonary vasodilators and BPA, have made the management of CTEPH more personalized. A MDT approach is now essential for optimal treatment, with PEA being the gold standard for operable cases. BPA and riociguat are options for inoperable patients or those with remaining PH after surgery. Future research should focus on long-term efficacy of these therapies, explore the genetic underpinnings of CTEPH, and develop non-invasive diagnostic tools. Additionally, clinical trials are needed to evaluate new combination therapies and the effectiveness of multidisciplinary care models, ensuring optimized and personalized treatment strategies for all patients.

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